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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/736,264	HARTIG ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/14/04;6/10/04;*. 6/23/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending. Claims 1-14 and 17-20 are under consideration in the instant office action.

Election/Restrictions

Applicant's election of Group I in the reply filed on March 10, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 10, 2006.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-6 are vague and indefinite because it is unclear from the claim language what kind of percentage (w/w %, w/v%, mole %, etc.) Applicant is referring to with regards to the recited amount of active agents. Appropriate correction is required.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 8, and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Keller et al. (U.S. Patent No. 6,475,467).

Keller discloses **medicinal aerosol formulations** incorporating solid, pharmaceutically acceptable **salts of cromoglycic acid and/or nedocromil** as carriers in therapeutically and prophylactically inefficacious amounts in suspension aerosol formulations **of pharmaceutical active compounds**. The carriers used increase the chemical and physical stability of moisture-sensitive active compounds and permits the abandonment of surface-active agents (title and abstract).

Keller discloses that the pharmaceutical active compound may be mixed with a pharmaceutically acceptable carrier (e.g. salts of cromoglycic acid and/or nedocromil) **to obtain a powder mixture**, which can be readily suspended in customary propellants (col. 4, lines 40-45).

Keller discloses that suitable pharmaceutical active compounds include any that can be administered as suspension aerosols, wherein preferred actives include betamimetics and anticholinergics. Examples of preferred actives include **salmeterol xinafoate** (col. 5, line 29) and **tiotropium bromide** (col. 5, line 32). If desired the aerosol formulations can also contain **two or more pharmaceutically active compounds** (col. 5, lines 13-16, 29, 32, and 36-45). The preferred aerosol formulations as a rule contain **approximately 0.0001 to 0.2% by weight of suspended active compound** (col. 5, line 67 and col. 6, lines 1-4).

Regarding the characteristic X-ray diffraction values, compacted bulk volume, and a melting point of 124 °C of salmeterol xinafoate recited in claims 3, 4, and 10, respectively, these characteristics are inherently a property of salmeterol xinafoate in powder form.

Claims 1, 3, 4, 10, 11, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Rand (US 2002/0189612).

Rand discloses a medicament dispenser suitable for use as an inhalation device (tile and [0001]), wherein in one embodiment the **medicament** is pre-metered prior to actuation of the dispenser by the patient, for example, in **capsules** [0037].

Rand discloses that the dispenser is suitable for dispensing medicament, particularly for the treatment of respiratory disorders, including asthma and COPD [0180]. Appropriate medicaments for use in the dispenser may be selected from drugs including bronchodilators (e.g. salmeterol) and anticholinergics (e.g. tiotropium). Rand discloses that it will be clear to a person skilled in the art that the medicaments may be used in the form of salts, esters, or as solvates to optimize the activity and/or stability of the medicament [0181]. Medicaments may also be used

in combinations, wherein preferred combinations include **salmeterol as the xinafoate salt** and an anti-inflammatory steroid [0182]. The dispenser's medicament container may comprise **medicament in dry powder form**, wherein said dry powder medicament may also further comprise a pharmaceutical excipient also in dry powder form [0184]. In other embodiments, the dry powder medicament particles are aerodynamically shaped to improve medicament delivery to the patient [0186] and the medicament may be in solution or suspension form [0187].

Regarding the characteristic X-ray diffraction values, compacted bulk volume, and a melting point of 124 °C of salmeterol xinafoate recited in claims 3, 4, and 10, respectively, these characteristics are inherently a property of salmeterol xinafoate in powder form.

Claims 1-10 and 17-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Richards (WO 03/013633).

Richards discloses an inhalation device with a pharmaceutical composition comprising plural doses of **medicament in powder form**, wherein the medicament comprises **salmeterol** and an **anticholinergic agent** or a **pharmaceutically acceptable salt**, solvate, or pharmaceutically functional derivative thereof. The compositions also contain a **pharmaceutically acceptable carrier or excipient** and may optionally comprise one or more other therapeutic ingredients (abstract and title).

Richard discloses that in one aspect the formulation comprises **salmeterol xinafoate**, an anticholinergic agent, a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients (pg. 3, lines 6-8). Suitable anticholinergics include, **tiotropium bromide** (pg. 3, lines 10-12). In another aspect the formulation is **suitable for**

administration by inhalation, and preferably is a dry powder (pg. 3, lines 14-16). Richards invention also includes both the (S) and (R) enantiomers of salmeterol and the anticholinergic agents either in substantially pure form or admixed in any proportions (pg. 3, lines 23-35). Richard's invention also provides methods for the treatment or prophylaxis of a disease associated with reversible airways obstruction, including asthma and COPD (pg. 10, lines 10-13). As a monotherapy, salmeterol xinafoate is generally administered to adult humans by **aerosol inhalation at a dose of 50 micrograms to 100 micrograms** twice daily, whereas a monotherapy of tiotropium is administered to adult humans by inhalation at **a dose from 18 micrograms to 200 micrograms** (pg. 10, lines 19-24). Formulations for inhalation include powder compositions, which will preferably contain lactose (pg. 11, lines 21-22). Examples 1-12 indicate that Richard's pharmaceutical compositions will generally comprise **12.5 mgs to 25.0 mgs of lactose**. Lactose is a disaccharide.

Regarding the characteristic X-ray diffraction values, compacted bulk volume, and a melting point of 124 °C of salmeterol xinafoate recited in claims 3, 4, and 10, respectively, these characteristics are inherently a property of salmeterol xinafoate in powder form.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Keller et al. (U.S. Patent No. 6,475,467).

The disclosures/teachings of Keller have been set forth above.

Keller does not anticipate claim 7, because a combined amount of tiotropium and salmeterol xinafoate of from 5-5,000 micrograms is not expressly disclosed.

The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal

amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

Claims 2 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rand (US 2002/0189612) in view of Banerjee et al. (US 2002/0289612).

The disclosures/teachings of Rand have been set forth above.

Rand lacks the teaching of tiotropium having a counter-ion selected from among chloride, bromide, iodide, methanesulfonate, or *para*-toluenesulfonate.

Banerjee teaches bronchodilating compositions and methods intended for administration as a nebulized **aerosol**, wherein the composition may contain formoterol or a derivative thereof and the compositions are useful in the methods of treating bronchoconstrictive disorders (abstract). Banerjee defines aerosol as meaning, **a liquid or particulate matter dispersed in air**, including dispersions of liquids and solids, including **powders**, in air [0021]. The compositions comprise a bronchodilating agent, including **salmeterol** [0008]. The bronchodilating compositions used in methods of treating, ameliorating, or preventing bronchoconstrictive disorders may further include the administration of an anticholinergic agent simultaneously with the bronchodilating composition [0076]. Suitable anticholinergic agents include **tiotropium bromide** [0080].

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Rand and Banerjee, because both inventors teach compositions comprising salmeterol and tiotropium to treat respiratory disorders. A skilled

artisan would have been further motivated to combine the teachings of Rand and Banerjee, because Rand discloses a medicament dispenser inhalation device suitable to dispense a composition comprising tiotropium and salmeterol. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because the administration of pharmaceutical compositions comprising a betamimetic and an anticholinergic via an inhalation device is well-known in the art and because tiotropium bromide is a well-known salt of tiotropium.

Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richards (WO 03/013633) in view of Rand (US 2002/0189612).

The teachings of Richards have been set forth above.

Richards teaches the amount of composition comprising salmeterol xinafoate and tiotropium bromide, but lacks the express teaching of the composition in a capsule.

The teachings of Rand have been set forth above.

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Richards and Rand, because both inventors teach pharmaceutical compositions comprising salmeterol xinafoate and tiotropium suitable for use in methods of treating respiratory diseases, wherein said compositions are in the form of powders. A skilled artisan would have been further motivated to combine said prior art teachings because both Richards and Rand teach inhalation devices containing said compositions which may be used in the treatment of respiratory diseases. Regarding the amount of composition contained within a capsule, the amount of a composition in a capsule is clearly a result effective parameter that a

person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of a composition needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of the amount of a pharmaceutical composition in a capsule would have been obvious at the time of applicant's invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 10, and 17-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,630,466

(USPN '466). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. Both claim sets recite pharmaceutical compositions comprising salts of tiotropium bromide and salmeterol xinafoate. Although the claims of USPN '466 do not recite the characteristic X-ray diffraction intensities, bulk volume, or melting point of salmeterol xinafoate, it would have been apparent that these are properties of salmeterol xinafoate in the powdered form. USPN '466 also does not recite said compositions as a powder, however, powdered forms of compositions comprising tiotropium and salmeterol are well-known (See Richards (WO 03/013633) and the term "pharmaceutical composition" of USPN '466 encompasses all composition forms. Finally, it is noted that USPN '466 has the same assignee as the instant application. Therefore, claims 1-7, 10, and 17-20 of the instant application are *prima facie* obvious over claims 1-5 of U.S. Patent No. 6,630,466.

Claims 1-6, 8, 10, and 17-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 13, and 14 of U.S. Patent No. 6,919,325 (USPN '325). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. Both claim sets recite pharmaceutical compositions comprising salts of tiotropium bromide and salmeterol xinafoate (i.e. the salt of 2-hydroxy-1-napthoic acid) in the form of a powder. Although the claims of USPN '325 do not recite the characteristic X-ray diffraction intensities, bulk volume, or melting point of salmeterol xinafoate, it would have been apparent that these are properties of salmeterol xinafoate in the powdered form. Therefore, claims 1-6, 8, 10, and 17-18

of the instant application are *prima facie* obvious over 1-3, 13, and 14 of U.S. Patent No. 6,919,325.

Claims 1-7 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, and 7-11 of copending Application No. 10/054,567 (copending '567) in view of Richards (WO 03/013633). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. Both sets of cited claims recite pharmaceutical compositions comprising a tiotropium salt and a salt of salmeterol. Copending '567 lacks the recitation of salmeterol xinafoate. This deficiency is cured by the teachings of Richards, set forth above, which teaches compositions comprising tiotropium bromide and salmeterol xinafoate. It would have been obvious to a person of ordinary skill in the art that one could use different salts of salmeterol in a pharmaceutical composition, including salmeterol xinafoate. Therefore, claims 1-7 of the instant application are prima facie obvious over claims 1, 2, 4, and 7-11 of copending '567 in view of Richards.

This is a provisional obviousness-type double patenting rejection.

Claims 1-6 and 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 7 of copending Application No. 11/056,968 (copending '968). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. Both claim sets recite compositions comprising a tiotropium salt

(e.g. tiotropium bromide) and a salmeterol salt (e.g. xinafoate (i.e. 2-hydroxy-1-napthoic acid)). Therefore claims 1-6 and 10 of the instant application are *prima facie* obvious over claims 1-3 and 7 of copending '968.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Other Matter

The Examiner respectfully suggests inserting a space between the following numbers and their corresponding units of measurement: 5,000 (μg); 20 (mg); 6 (mg); 12 (mg), in claims 7, 12, 13, and 14, respectively. To remove any possibility of ambiguity, the Examiner respectfully suggests including the units of measurement for the lower limit values in the ranges of the amount of active agent recited in claims 7 and 12-14.

Conclusion

Claims 1-14 and 17-20 are rejected. All claims under consideration in the instant office action are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph.D.
Examiner

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER